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Successful Management With Octreotide of a Child With L-Asparaginase Induced Hemorrhagic Pancreatitis

Tim Garrington, MD,[1] Denis Bensard, MD,[1,2] J. David Ingram, MD,[3] and Christopher C. Silliman, MD, PhD[1,2,4,*]

Background. Octreotide is a synthetic somatostatin analogue which has been suggested for use in the management of acute pancreatitis. While studies have looked at octreotide use in the setting of pancreatitis due to chronic alcohol use or trauma, little is known of its role in management of drug induced acute pancreatitis, particularly in the pediatric setting.

Patients and Methods. We present a case of a 5½-year-old white female who developed severe, necrotizing, hemorrhagic pancreatitis with pseudocyst formation secondary to L-asparaginase use as a part of her therapy for acute lymphoblastic leukemia (ALL). She was managed initially with intravenous fluids, bowel rest, nasogastric suctioning, parenteral narcotices, and broad spectrum antibiotics. In addition, within 12 hours of admission to The Children's Hospital (TCH) in Denver, Colorado, she began therapy with octreotide (5 micrograms/kg/day IV divided b.i.d.). With this management, her pseudocyst decompressed without need for surgical intervention, her pancreatitis fully resolved, and she recovered full pancreatic function without any long-term sequelae.

Conclusion. Use of octreotide may have served a role in limiting the severity of the disease process in this case. Further studies need to be done to verify its usefulness in this setting. Med. Pediatr. Oncol. 30:106–109, 1998.
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Key words: octreotide; acute pancreatitis; L-asparaginase

INTRODUCTION

Acute pancreatitis is a well described complication of L-asparaginase therapy for acute lymphoblastic leukemia (ALL) [1]. Nguyen *et al* reported a 7% incidence of pancreatitis, as detected on serial sonograms, in children being treated with L-asparaginase [2]. In addition, children with ALL are usually also treated with corticosteroids, which have a probable association with pancreatitis [1]. Use of these drugs in combination puts patients being treated for ALL at significant risk for development of acute pancreatitis.

L-asparaginase induced pancreatitis is a relatively benign disease with few complications in 80–90% of cases [3]. In a small percentage of cases, however, necrotizing pancreatitis can develop, with more severe complications resulting in a significant mortality risk. Complications include hemorrhage, pseudocyst formation, pancreatic insufficiency (both exocrine and endocrine), sepsis, and respiratory distress due to pulmonary edema or pleural effusion. Treatment of drug induced acute pancreatitis consists of discontinuation of the offending drug combined with aggressive patient support, including bowel rest, nasogastric suctioning, parenteral nutrition, pain management with parenteral narcotics, and broad spectrum antibiotics. Pancreatic pseudocysts may spontaneously resolve; however, if recalcitrant, these pseudocysts require percutaneous drainage.

Recently, octreotide, a synthetic somatostatin analogue, has been suggested for use in the management of pancreatitis [4–7]. Somatostatin is a naturally occurring oligopeptide produced primarily in the gastrointestinal tract which has multiple effects, including inhibition of pancreatic enzyme secretion, growth hormone release, pancreatic islet release of insulin and glucagon, and secretion of gastrin and vasoactive intestinal polypeptide (VIP) secretion by the gut. In addition, somatostatin decreases emptying time of the stomach and gall bladder as well as generally inhibiting gut motility [8]. Because of their direct effects on the pancreas, somatostatin and oc-

[1]Department of Pediatrics, The University of Colorado School of Medicine, Denver, Colorado.

[2]Department of Surgery, The University of Colorado School of Medicine, Denver, Colorado.

[3]Department of Radiology, The Children's Hospital, Denver, Colorado.

[4]The Bonfils Blood Center, Denver, Colorado.

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*Correspondence to: Christopher C. Silliman, Research Department, Bonfils Blood Center, 717 Yosemite Circle, Denver, CO 80220.

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treotide have been used in the treatment of acute pancreatitis secondary to chronic alcohol use or trauma. Meta analysis of several small studies showed a significant decrease in mortality in patients treated with somatostatin [9]. However, due to its short half-life (2–3 minutes), continuous IV infusion is required to achieve the desired effect. Octreotide, which maintains the same physiologic effects as somatostatin, has a much longer half-life (113 minutes), allowing an intermittent dosing schedule. Moreover, it does not have the rebound endocrine hypersecretion seen with somatostatin following discontinuation of the drug [8]. Although octreotide has mainly been used in the treatment of adult patients, a few pediatric patients have been successfully managed with octreotide for nesidioblastosis and other hyperinsulinemic conditions, secretory diarrhea, or pancreatitis associated with abdominal trauma [10,11]. We report the use of octreotide to treat a case of severe, necrotizing, hemorrhagic pancreatitis caused by L-asparaginase in a patient with newly diagnosed ALL.

CASE REPORT

R.H. is a white female who presented at age 5½ years with a 3 week history of intermittent fevers, malaise, and both abdominal and leg pain. Her past medical history was unremarkable. Physical examination revealed a pale, ill appearing child in no acute distress. She did not have detectable adenopathy or hepatosplenomegaly. A CBC demonstrated a WBC count of 3900/mm^3 with 24% neutrophils, 3% band forms, 65% lymphocytes, 1% monocytes, and 7% blasts. Hemoglobin was 10.0 g/dl and the platelet count was 30,000/mm^3. A bone marrow biopsy revealed a large population of blast cells of L1 morphology. Flow cytometric studies of the marrow showed positivity for CD10 and Ia, consistent with precursor-B cell ALL. No leukemic cells were seen in the cerebrospinal fluid. Cytogenetic analysis of the blast cells was not informative.

Based on these findings, R.H. began a standard three-drug induction therapy regimen for standard risk ALL. Induction therapy consisted of four weekly doses of vincristine (1.5 mg/m^2), 28 days of prednisone (40 mg/m^2/day divided t.i.d.), intrathecal cytosine arabinoside given at day 0, intrathecal methotrexate given at day 14, and nine doses of E. coli L-asparaginase (6,000 IU/m^2) given intramuscularly three times weekly for three weeks starting on day 3 of therapy. She responded well to initiation of therapy, with rapid improvement of her abdominal and leg pain and with clearing of blasts from her peripheral blood. A day 14 bone marrow aspirate showed clearing of the blast cells with normal tri-lineage recovery.

Toward the end of induction therapy, following her final dose of L-asparaginase, R.H. developed abdominal discomfort with non-bilious, guaiac negative emesis. Her stools remained normal. She was seen by her primary care physician and treated with promethazine. Her abdominal symptoms worsened, and the following day she was admitted to her local hospital for IV rehydration and observation. During the hospitalization she developed peritoneal signs, necessitating on exploratory laparotomy for suspected appendicitis. Exploration of the peritoneal cavity revealed a normal appendix; however, a large right-sided retroperitoneal hematoma was present. No further interventions were performed, and the incision was closed. Arrangements were then made for transfer to The Children's Hospital (TCH) in Denver, Colorado. At that time, her blood hemoglobin level had dropped from 10.0 gms% to 9.1 gms%. She was tachypnic and tachycardic, with a stable blood pressure and adequate perfusion.

On arrival at TCH, she received fluid resuscitation with crystalloid, colloid, and packed red blood cells. Physical examination at that time showed her to be alert, with complaints of severe abdominal pain. She remained tachypnic and tachycardic, with a blood pressure of 108/49. Examination of the abdomen revealed a positive Cullen's sign (bluish discoloration of the periumbilical region, indicative of tracking blood-stained retroperitoneal fluid along the falciform ligament) [12], with hypoactive bowel sounds and guarding but without rebound tenderness. Significant laboratory studies included normal serum electrolytes, renal function studies, and hepatocellular enzyme levels. The serum amylase was 493 IU/L (normal range: 48–138 IU/L), and serum lipase was 1892 IU/L (normal range: 7–60 IU/L). A chest radiograph showed a left pleural effusion. A CT scan of the abdomen demonstrated an enlarged pancreas with an adjacent pseudocyst and ascites (Figure 1A).

Based on these findings, she was diagnosed with acute, necrotizing, hemorrhagic pancreatitis with a pseudocyst. Initial management included nasogastric tube placement with suctioning, bowel rest, analgesics, and broad spectrum antibiotics. Intravenous hyperalimentation was also begun. Drainage of the pseudocyst was considered, but because of fears of high morbidity with surgical intervention, the patient was managed conservatively. With hopes of reversing her clinical course and minimizing her risk of further complications, she was begun on intravenous octreotide (5 micrograms/kg/day divided b.i.d.). Octreotide therapy was initiated within 12 hours of arrival at TCH. The following day, R.H.'s hemoglobin level dropped to 6.9 gms%, and a repeat CT scan showed increased size of the pseudocyst due to hemorrhage. She was supported with blood products and closely observed. Following this initial period, R.H.'s condition stabilized. She did develop worsening of the left pleural effusion, which required drainage on day 4 of her hospitalization. Over hospital days 4–8 her clinical status showed steady improvement as evidenced by decreasing levels of serum amylase and lipase to 27 IU/L

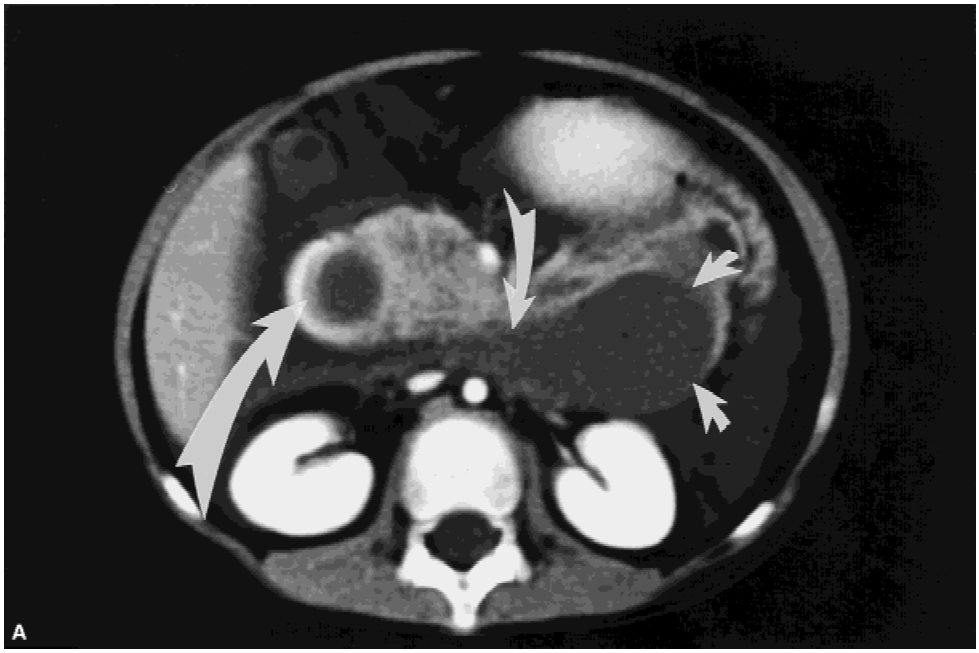

Fig. 1A. A large pseudocyst involves the head of the pancreas (large arrow) as well as extends below the tail (small arrows). The pancreatic body (intermediate arrow) is edematous.

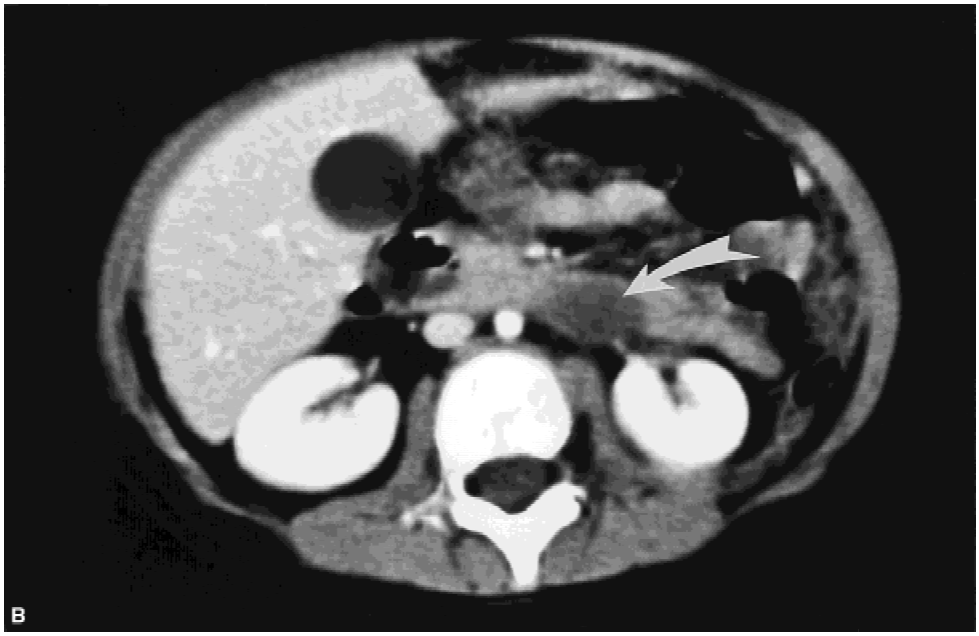

Fig. 1B. A small pseudocyst (arrow) remains in the body of the pancreas. Note that the level of the CT scan in 1B is different than in 1A to show the widest diameter of the pseudocyst in each case.

and 50 IU/L, respectively. Following seven days of therapy, octreotide was discontinued. A CT scan of the abdomen on day 9 showed a marked decrease in the size of the pseudocyst. Three weeks later, the pseudocyst had almost completely resolved (Figure 1B). She continued to require parenteral morphine for 3 weeks and intravenous hyperalimentation for approximately a month. When she was able to tolerate oral nutrition, she was given pancrease with meals for a total of six weeks. She had no problems with steatorrhea or weight loss, and she remains in good health with no long-term sequelae from her episode of severe hemorrhagic pancreatitis. L-

asparaginase was deleted from her chemotherapeutic regimen. She has subsequently received multiple pulsatile courses of corticosteroids without any complications.

DISCUSSION

Octreotide has been used to treat multiple conditions, including carcinoid syndrome, pituitary tumors, Zollinger-Ellison syndrome, glucagonomas and insulinomas, diabetes mellitus, chronic diarrhea, dumping syndrome, pancreatitis and pancreatic pseudocysts [13]. Little is known about its use in drug-induced acute pancreatitis, particularly in the pediatric setting. The rationale for use of octreotide is that by inhibiting pancreatic exocrine function, autodigestion of the pancreas along with damage to surrounding tissues will be prevented. Octreotide has been found to be safe and effective for the treatment of acute pancreatitis in adults [7]. It has been found to have few adverse side effects, with soreness at the site of injection when given subcutaneously being the most common [7]. It has not been found to have any long-term effects on growth in children [10].

This case illustrates the potential usefulness of octreotide as part of the management of drug-induced acute hemorrhagic pancreatitis. Pancreatitis of this severity is historically associated with a significant degree of morbidity and mortality. While this patient did suffer acute complications of her pancreatitis, she did not suffer any life threatening complications or long-term sequelae. We were also able to manage the pseudocyst without surgical intervention, avoiding further morbidity. Use of octreotide may have served a role in limiting the severity of the disease process in this case. Further studies need to be done to verify its usefulness in this setting.

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